



Adaptive Design in Dose Ranging Studies Based on Both Efficacy and Safety Responses

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Outline

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Summary

Background

- “...Half of all drugs in Phase III programs never reach the market. This is actually a worse rate than even five or 10 years ago, when about 80 percent of drugs in Phase III development were marketed.” (Designing Adaptive Clinical Trials. An FDA News Management Report, 2007)

Many Phase III trials fail due to:

- Lack of safety and/or efficacy
 - Ineffective dose/regimen studied and/or ineffective patient population
 - Inadequate planned study design to demonstrate the desired treatment effect
-
- 20% of drugs approved by FDA between 1980 and 1989 had the initial dose changed (in most cases lowering it).

Background (Cont.)

- There are two approaches to dose-response studies
 - Estimating the dose-response relationship
 - Multiple comparisons of contrasts between doses
- Regulatory guidance indicates that there is a place for each of these approaches
 - E4 (“Dose Response Information to Support Drug Registration”) says there is a need to find a lowest dose with a discernible effect (*sounds like paired comparison*), but that dose response study designs should emphasize the “elucidation of the dose-response function”
 - E10 (“Choice of Control Group...”): if a significant trend is shown, *“further study may be needed to assess the effectiveness of low doses”*
 - E9, Section 3.3.3 : Trials to Show Dose-response Relationship
“...the application of procedures to estimate the relationship between dose and response, including the construction of confidence intervals and the use of graphical methods, is as important as the use of statistical tests”.

Theory and Methods

“Adaptive designs for dose-finding based on efficacy–toxicity response”
Journal of Statistical Planning and Inference, Volume 136, Issue 6,
June 2006, Pages 1800-1823

Vladimir Dragalin and Valerii Fedorov

“Adaptive designs for selecting drug combinations based on efficacy-toxicity response”, *Journal of Statistical Planning and Inference*, In Press, Accepted Manuscript, Available online 19 June 2007

Vladimir Dragalin, Valerii Fedorov and Yuehui Wu

Big thanks to authors for sharing their work before it was published!

Theory and Methods (Cont.)

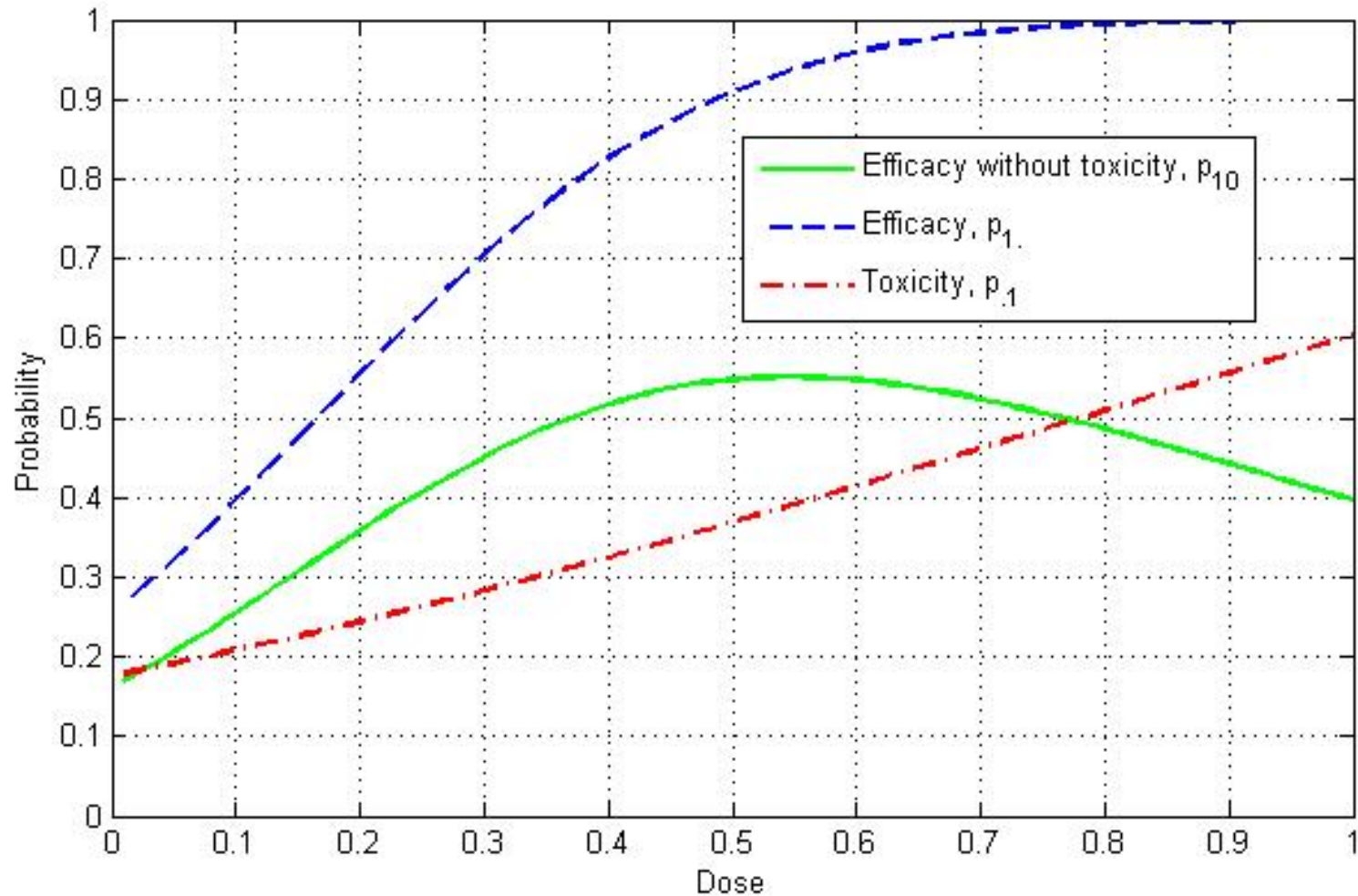
Distribution of bivariate binary endpoint is modeled

- using Gumbel bivariate logistic regression and Cox bivariate binary model for one drug dose responses
- using bivariate probit model for drug combination dose responses

$$p_{yz}(x, \theta) = \Pr(Y = y, Z = z | D = x), \quad y, z = 0, 1$$

		Toxicity Z		
		1	0	
Efficacy Y	1	p_{11}	p_{10}	$p_{1.}$
	0	p_{01}	p_{00}	$p_{0.}$
		$p_{.1}$	$p_{.0}$	1

Dose-Response Curves



Theory and Methods (Cont.)

- **2D Probit Model:**

$$p_{11}(x, \theta) = \Phi[\eta_1(x, \theta), \eta_2(x, \theta); \rho],$$

$$p_{1\bullet}(x, \theta) = \Phi[\eta_1(x, \theta)],$$

$$p_{\bullet 1}(x, \theta) = \Phi[\eta_2(x, \theta)],$$

$$p_{10} = p_{1\bullet} - p_{11},$$

$$p_{01} = p_{\bullet 1} - p_{11}.$$

$$\Phi[\eta_1(x, \theta), \eta_2(x, \theta); \rho] = \int_{-\infty}^{\eta_1} \int_{-\infty}^{\eta_2} \frac{1}{2\pi\sqrt{1-\rho^2}} e^{\frac{-z_1^2 - 2\rho z_1 z_2 + z_2^2}{2(1-\rho^2)}} dz_1 dz_2,$$

$$\Phi[\eta] = \int_{-\infty}^{\eta} \frac{1}{\sqrt{2\pi}} e^{-z^2/2} dz.$$

Theory and Methods (Cont.)

- Fisher Information Matrix provides the basis for the optimality criterion and determines the patient allocation in the study.
- Information Matrix for a single observation

$$\mu(x, \theta) = \frac{\partial p}{\partial \theta} (P - pp^T)^{-1} \frac{\partial p}{\partial \theta^T},$$

$$p = \begin{pmatrix} p_{11} \\ p_{10} \\ p_{01} \end{pmatrix},$$

$$P = \begin{pmatrix} p_{11} & 0 & 0 \\ 0 & p_{10} & 0 \\ 0 & 0 & p_{01} \end{pmatrix}$$

Theory and Methods (Cont.)

- **Total Information and Penalty**

$$M(\xi, \theta) = \sum_{i=1}^n r_i \mu(x_i, \theta)$$

$$\Phi(\xi, \theta) = \sum_{i=1}^n r_i \varphi(x_i, \theta)$$

$$\text{Var}(\hat{\theta}) = D(\xi, \theta) \approx M^{-1}(\xi, \theta)$$

Theory and Methods (Cont.)

- **Locally Optimal Design**

$$\xi^*(\theta) = \arg \min_{\xi} \Psi[D(\xi, \theta)]$$

D-optimality: find a design such that

$$\xi^*(\theta) = \arg \max_{\xi} |M(\xi, \theta)|$$

A design ξ^* is locally D-optimal if and only if

$$d(x, \xi^*, \theta) = \text{tr}[\mu(x, \theta)M^{-1}(\xi^*, \theta)] \leq m,$$

$d(x, \xi^, \theta)$ is called "sensitivity function"*

m is the total number of parameters

Theory and Methods (Cont.)

■ Composite/Bayesian Design

- Randomize n subjects according to initial design
- Estimate unknown parameters and build var-cov matrix/use priors
- The optimal criterion becomes:

$$\xi^* (\hat{\theta}, \Sigma_0) = \arg \max_{\xi} \log | \Sigma_0^{-1} + MN(\xi, \hat{\theta}) |$$

■ Adaptive Design

At each step select the dose which is the most informative given the accumulated knowledge. Continue the process until the desired level of precision of the dose response model parameters is achieved, or the total number of patients had been allocated.

For large N adaptive designs provide approximately the same precision as locally optimal designs.

Theory and Methods (Cont.)

- **Restricted Design Region**

$$X(\theta) = \{x : \text{probability of efficacy} \geq Q_E; \text{probability of toxicity} \leq Q_T\}$$

- **Penalized Design**

Penalty function

$$\varphi(x, \theta, E, T) = \{p_{10}(x, \theta)\}^{-E} \{1 - p_{.1}(x, \theta)\}^{-T}$$

Optimization criterion becomes

$$\xi^*(\theta) = \arg \max_{\xi} |M(\xi, \theta)|$$

under the constraint on the total penalty

$$\Phi(\xi, \theta) = \int \phi(x, \theta) \xi(dx) \leq \Phi^*$$

Examples: Case Study 1

Indication:

- Acute (post-operative) pain

Objective of the study:

- To provide the information on the dose response relationship of the drug combination

Regulatory requirement for a confirmatory trial:

- To show superiority compare to each drugs at the same dose or non-inferiority with the lower dose combination

Clinical Evidence:

There are evidence that the combination will show the superiority, but might have undesirable safety profile. Dose-response study to explore the combination relationship is necessary.

Examples: Case Study 1

Drug 1:

- 100 mg/day, 200 mg/day, and 400 mg/day (BID and QD)

[Capsules: 50 mg, 100 mg, 200 mg, 400 mg]

Drug 2:

- 150 mg/day, 300 mg/day, and 600 mg/day (BID)

[Capsules: 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, and 300 mg]

■ **Primary Efficacy Endpoint:**

– Response rate (responder definition is based on pain reduction and morphine consumption)

■ **Primary Safety Endpoint:**

– Incidence of Adverse Events of “special” interest

The efficacy and toxicity responses are binary

Examples: Case Study 1

- **The study is a good candidate for adaptive design:**
 - Response is available quickly (within the first 48 hours)
 - Not very fast recruitment
 - One or two sites with a total of ≈ 200 patients
- **Questions to answer:**
 - What method to use?
 - How many dose combinations are needed to be tested?
 - How to choose them?
 - How many patients to allocate at each dose combination (each stage)?

Examples: Case Study 1

- Method: Adaptive dose allocation based on locally D-optimality criterion for selecting drug combinations based on efficacy and toxicity response proposed by V.Dragalin and V.Fedorov
- Bivariate Probit Model based on the multivariate normal distribution was used.

$$p_{a,b}(x, \theta) = Pr(Y_E=a, Y_T=b | x, \theta),$$

for a, b in $\{0, 1\}$, $x=(x_1, x_2)$,

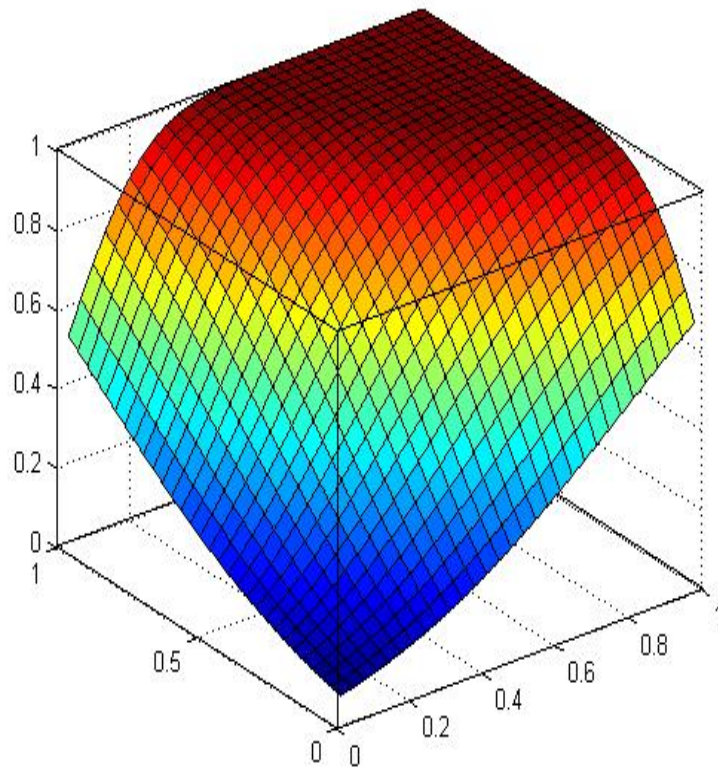
$$\Theta = (\theta_{11}, \theta_{12}, \theta_{13}, \theta_{14}, \theta_{21}, \theta_{22}, \theta_{23}, \theta_{24}, \rho)$$

Fit the model, and estimate Θ .

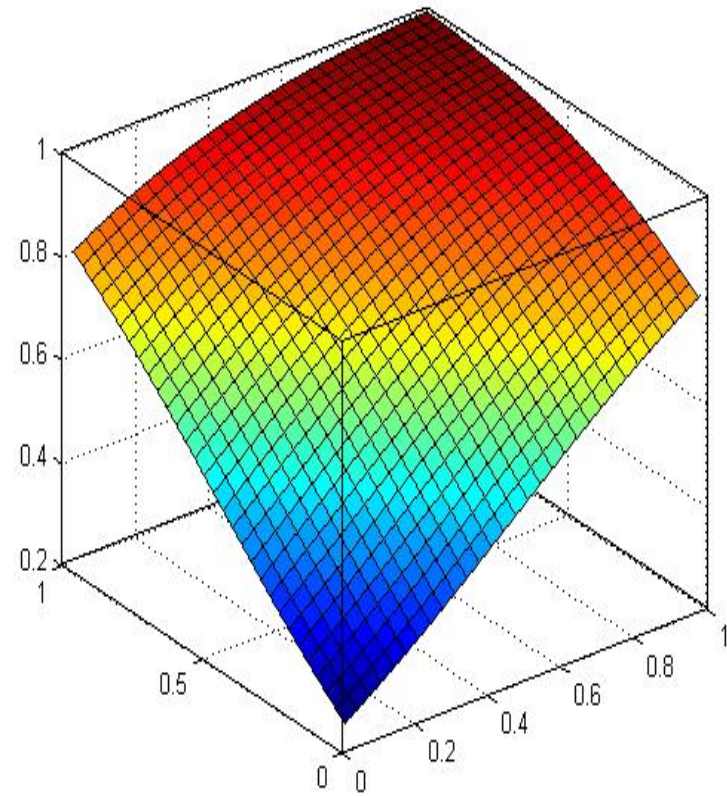
		Toxicity		
		1	0	
Efficacy	1	p_{11}	p_{10}	p_{1*}
	0	p_{01}	p_{00}	p_{0*}
		P_{*1}	P_{*0}	1

Response Probability Surfaces

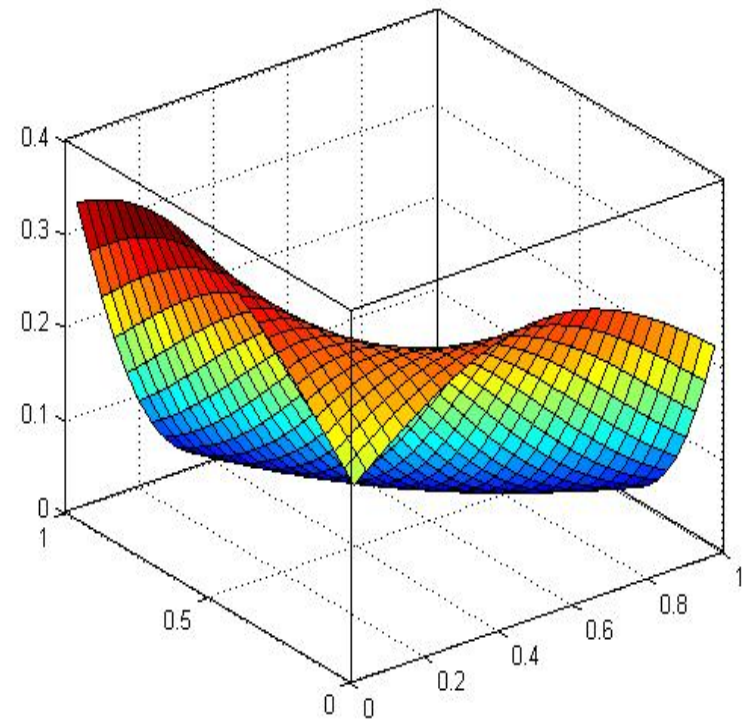
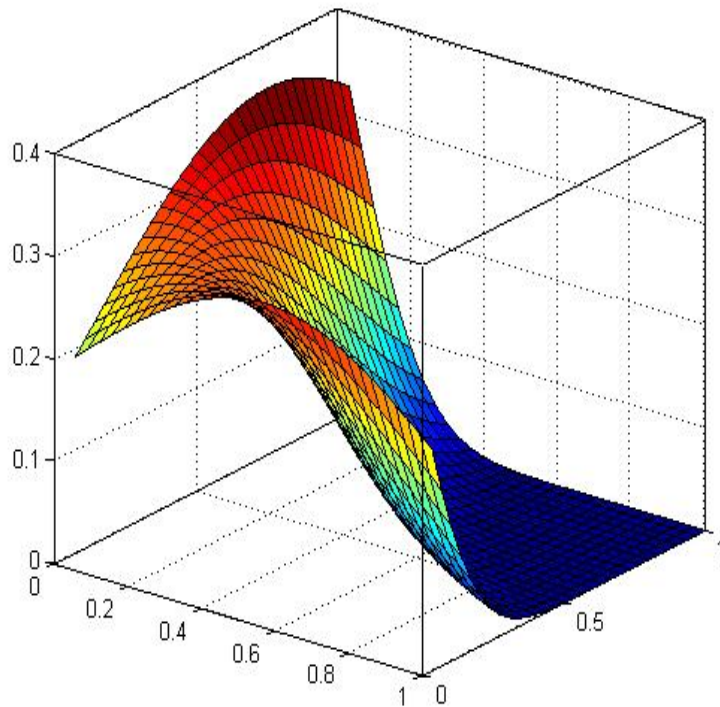
Efficacy: p_{1*}



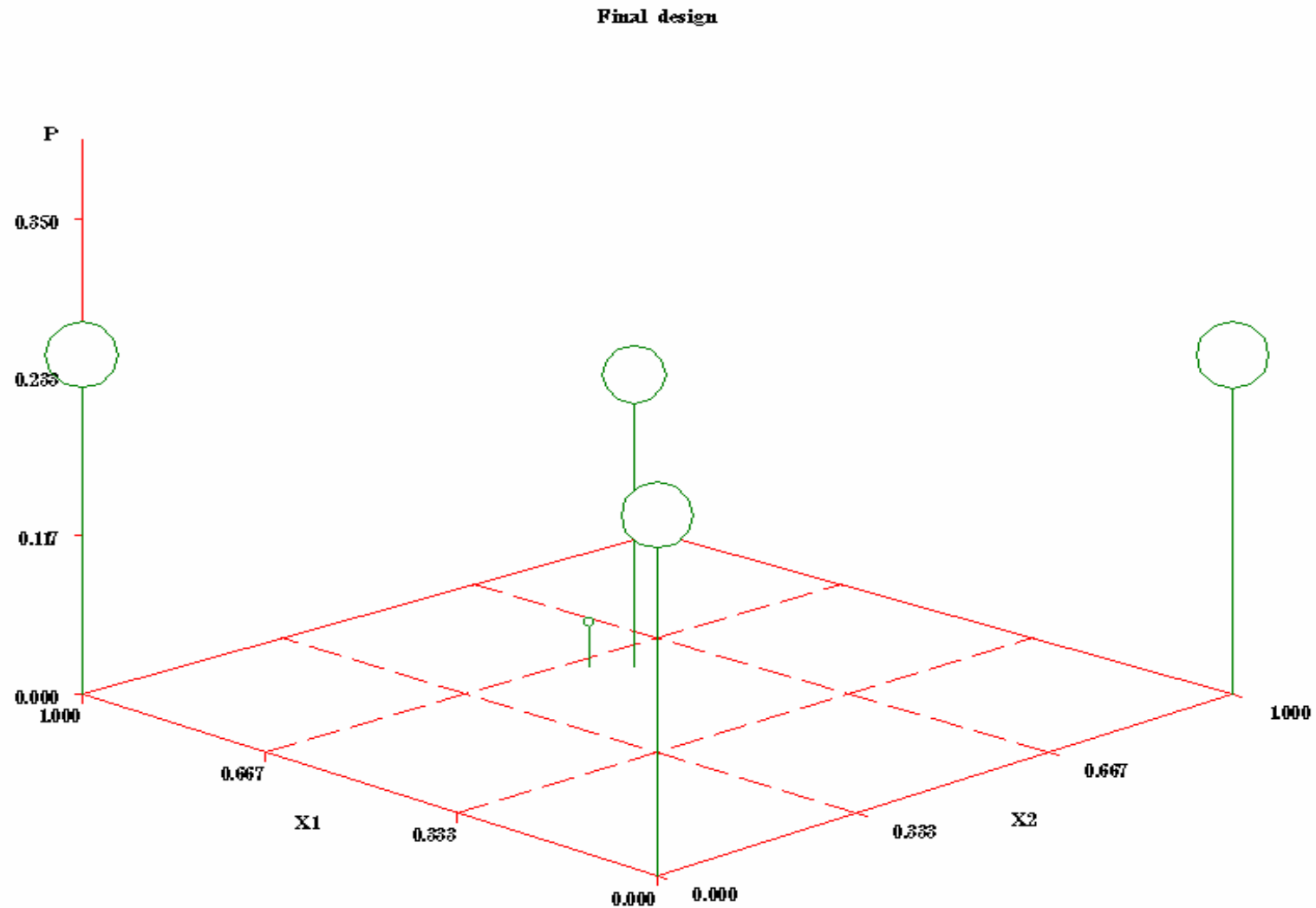
Toxicity: p_{*1}



Efficacy Without Toxicity: p_{10}

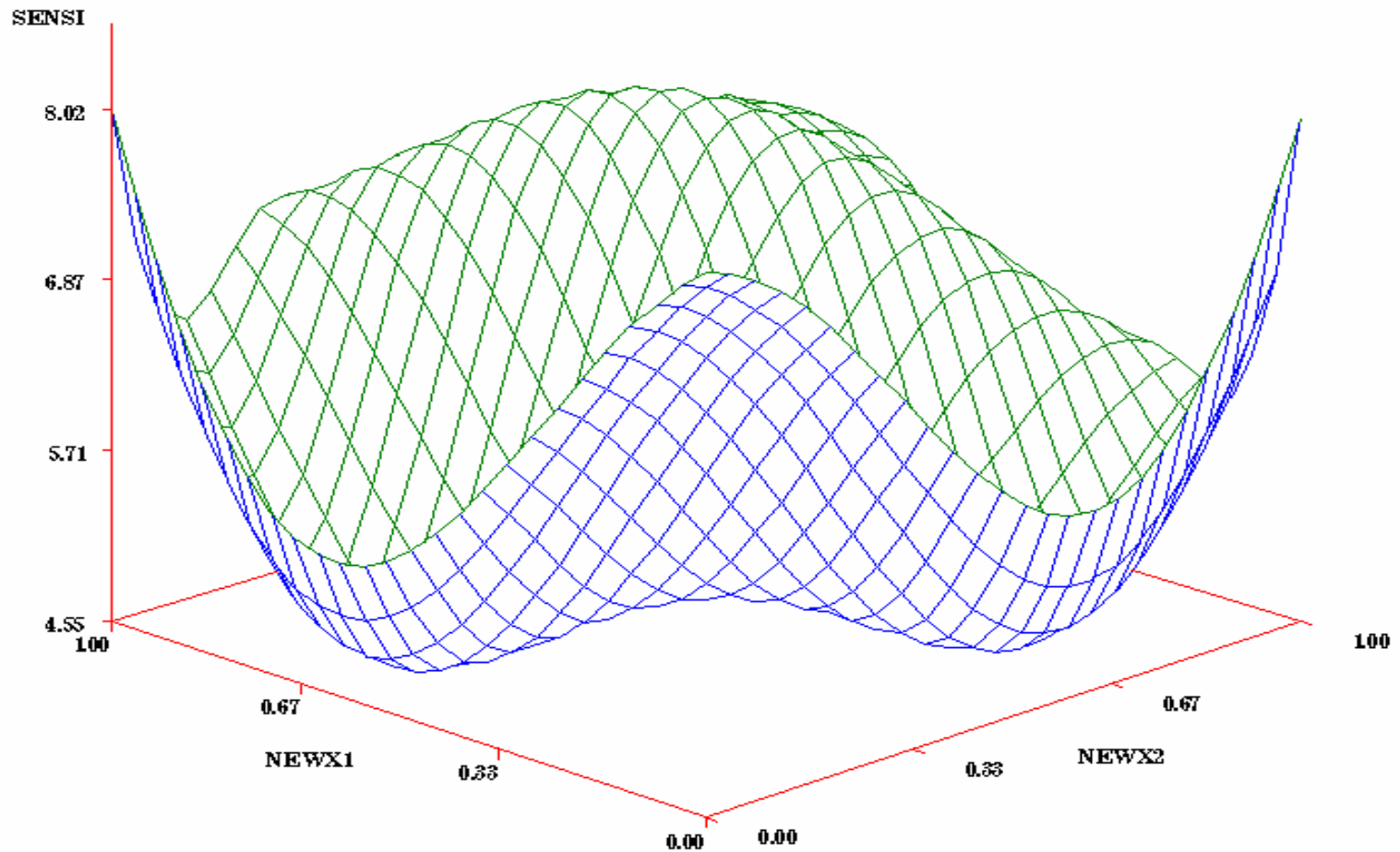


Locally Optimal Design



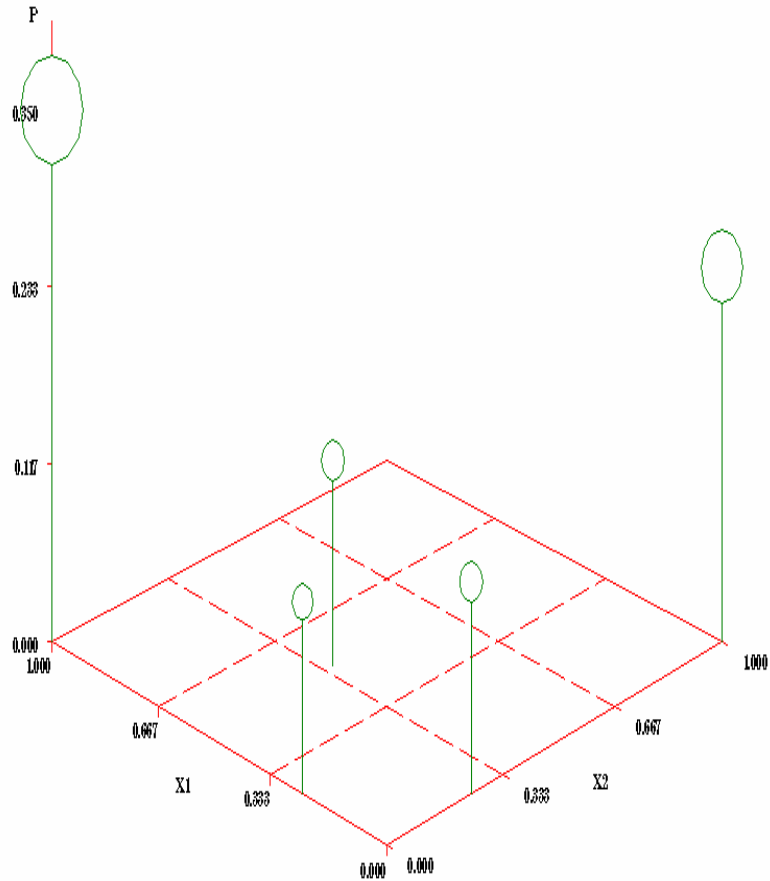
Locally Optimal Design

Sensitivity function, final design

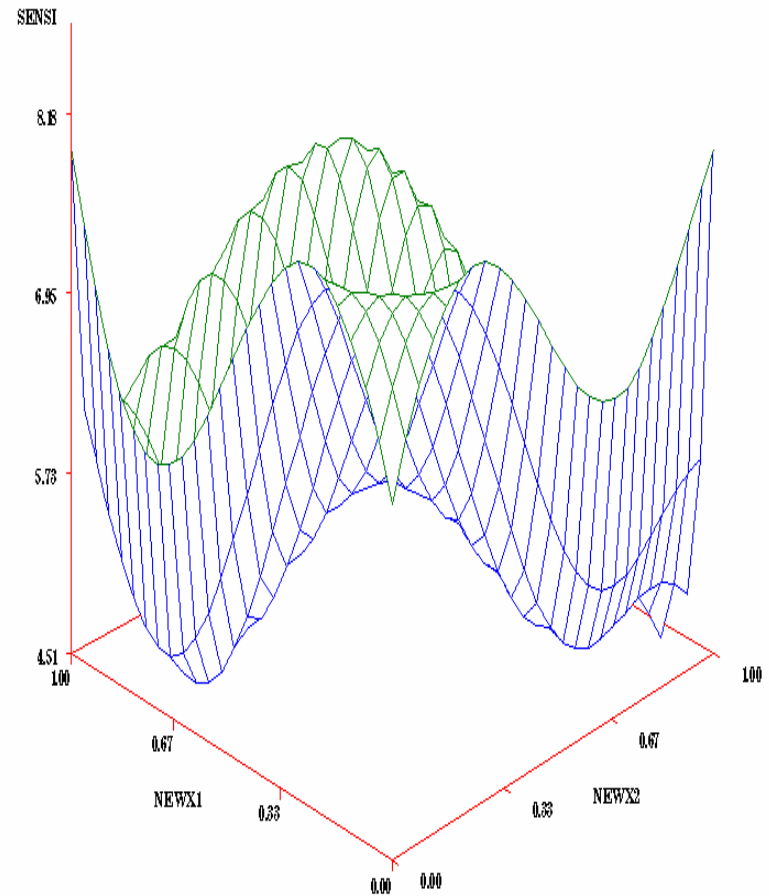


Restricted Locally Optimal Design: Efficacy > 0.2 and Toxicity < 0.8

The Final Design

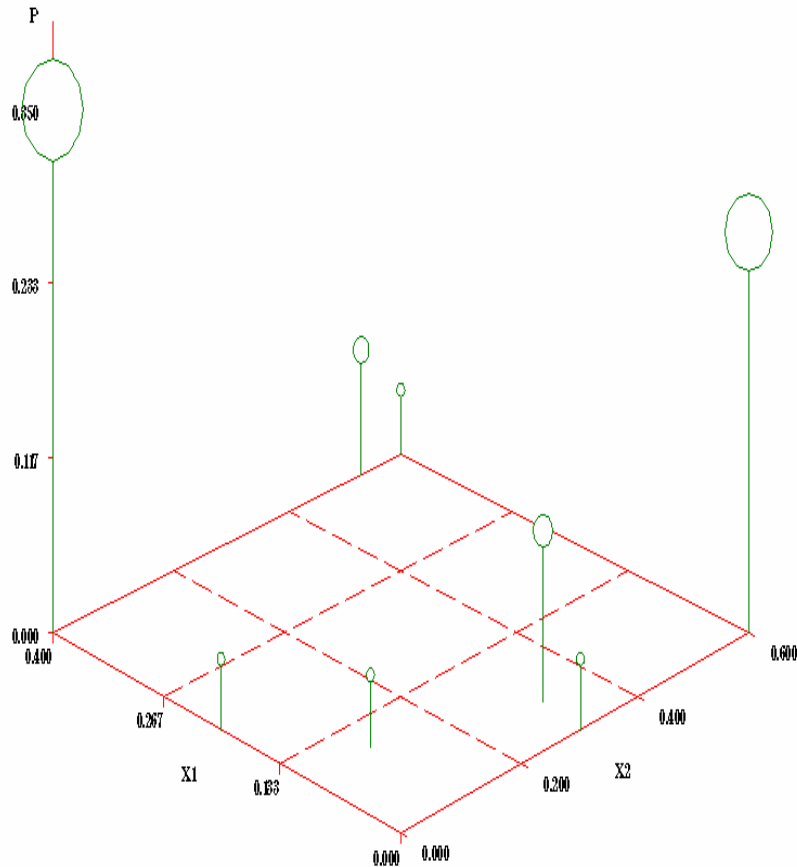


The Final Design

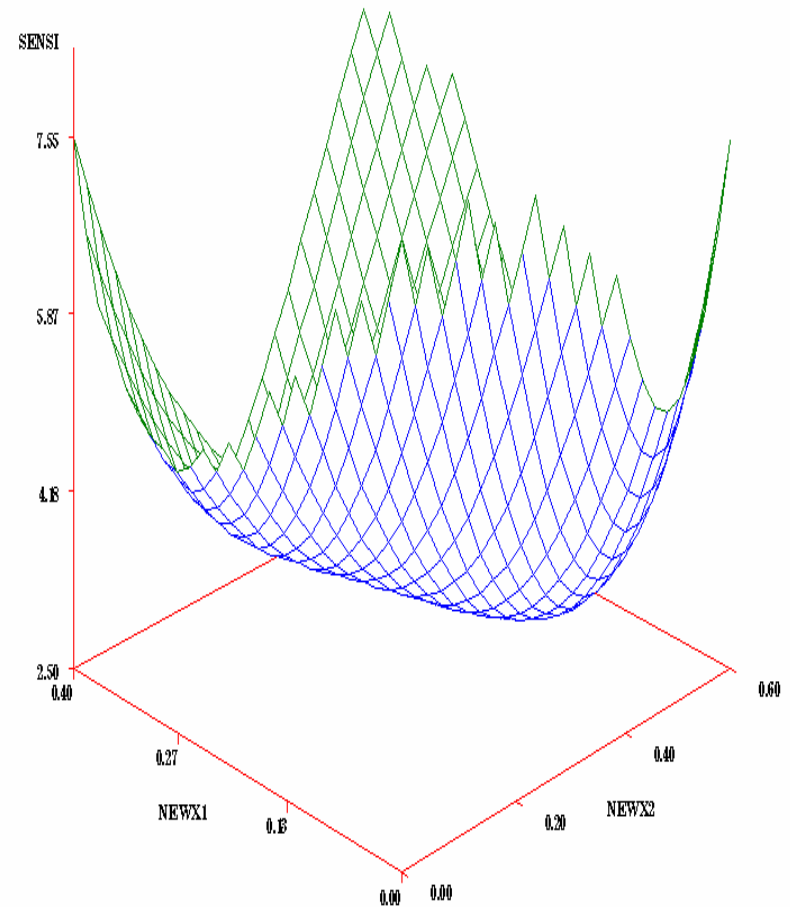


Restricted Penalized Locally Optimal Design: Efficacy > 0.2 and Toxicity < 0.8 , $E=1$ and $C=1$

The Final Design



The Final Design



Case Study 1

- The method was evaluated using
 - Different restrictions on safety and efficacy
 - Different penalties
 - Different initial designs/combinations
 - Several scenarios
 - Different restrictions on the total sample size

Examples: Case Study 2

Objective:

- To find a single dose to use for Phase 3 study that jointly maximizes the rates of efficacy response and minimizes the rates of AE of “special” interest (Cardiovascular TA)
- To provide the info on the dose relationship

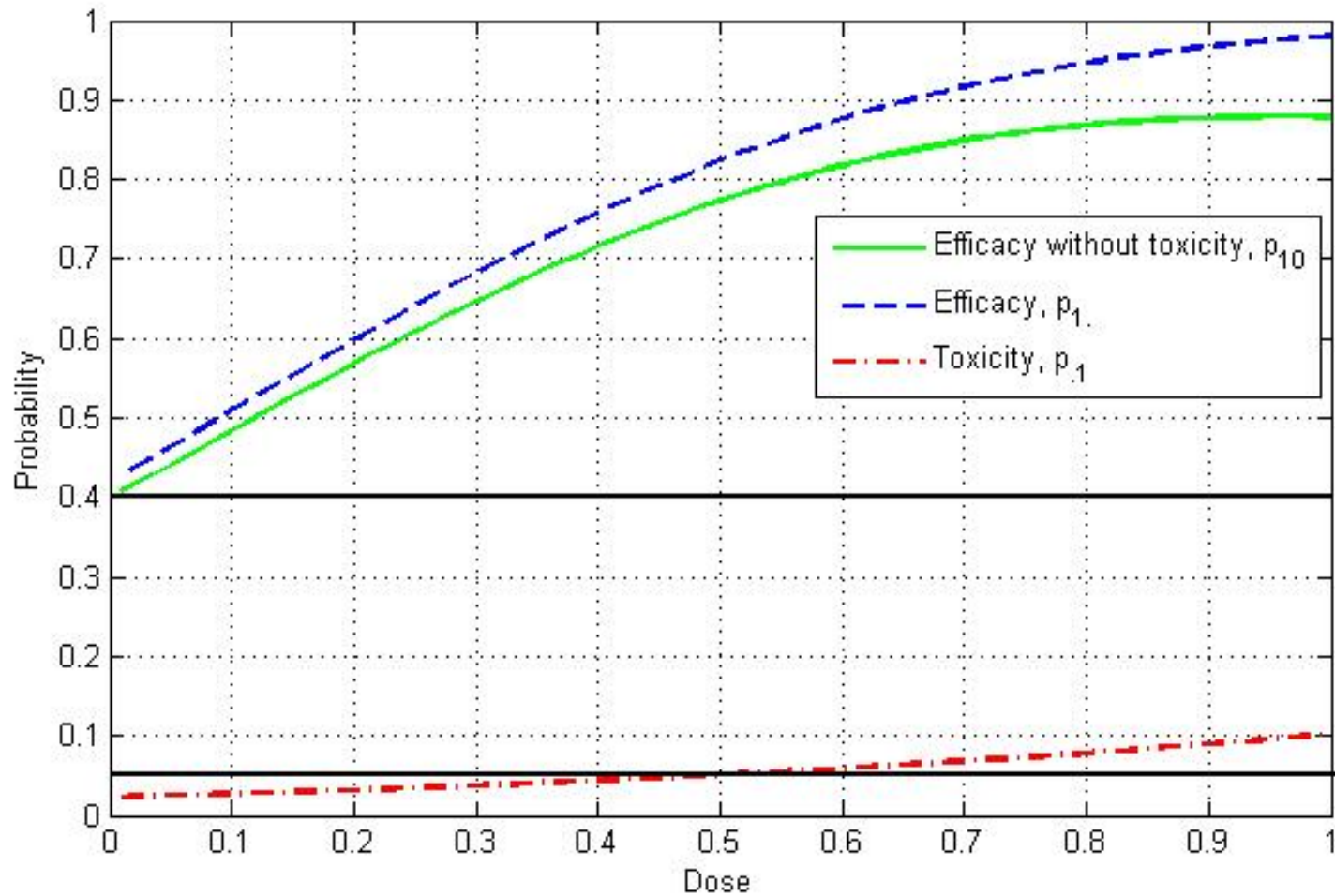
Preliminary Assumptions:

- 10 test drug doses, placebo and active comparator; chosen dose should have no less than 40% of efficacy incidence and no more than 5% of toxicity; estimated efficacy/toxicity are available from PK/PD modeling
- Primary efficacy and toxicity responses are binary.

Case Study 2

- Two adaptive methods were proposed and evaluated using simulations in EffTox and SAS:
 - Bayesian response-adaptive method based on trade-off contours approach using both efficacy and toxicity for dose-finding (see P.Thall and J.Cook, Biometrics, 2004)
 - Adaptive dose allocation based on locally D-optimality criterion for selecting optimal safe dose using efficacy and toxicity response (see V.Dragalin and V.Fedorov, Journal of Statistical Planning and Inference, 2006)

Case Study 2



Case Study 2

- Designs were evaluated using:
 - 5, 7, and 10 doses
 - Cohort size of 1, 3, 10, 20 patients
 - Different starting doses/designs
 - Total of 400 and 800 patients

In order to assess the sensitivity of the clinical trial simulation results to the data assumptions, three sets of assumptions were used. These relate to levels of predicted potency: either low (25th estimated percentile), 'best guess' (50th estimated percentile) or high (75th estimated percentile).

Case Study 2

- Simulations were summarized using:
 - probability of each dose being the final/OSD
 - average number of patients treated at each dose
 - expected toxicity at each dose
 - expected efficacy at each dose
 - expected efficacy without toxicity at each dose

The goal of the first method is to allocate patients to the safe doses in the trial (individual ethics), and in some cases, it lost in the accuracy of the estimation and consequently in selecting OSD. Adaptive design based on locally D-optimality criterion allocates one patient or cohort to “high risk” doses improving the accuracy of estimation and selection of OSD.

Summary

Strong Aspects of Method:

- Dose-finding based on both efficacy and toxicity
- Method is applicable to drug combinations, different type of responses
- Many more doses, and a broader range, can be tested
- Interpolation to doses not studied, but within the range of doses studied

Limitations of Method:

- No within-study direct comparisons with active control
- General software package for solving optimal design problems is not available

Summary (Cont.)

- Adaptive dose allocation based on locally D-optimality criterion is a good competitor to other designs
- 'Ineffective' doses are often very informative to learn about the dose-response profile
- Need to balance gains associated with adaptive dose ranging designs approach against greater methodological and operational complexity
- Trial simulations should be used for estimating operational characteristics of designs/methods.

The value of dose-response modeling

- Efficiency gain compared to pairwise comparisons (if number of subjects per treatment is low)
- More doses, and a broader range, can be tested
- Added info about doses not studied
- Valued by regulators in rational for dose selection in label, may avoid need to reduce dose after approval
- More attractive to patients

Regulatory References

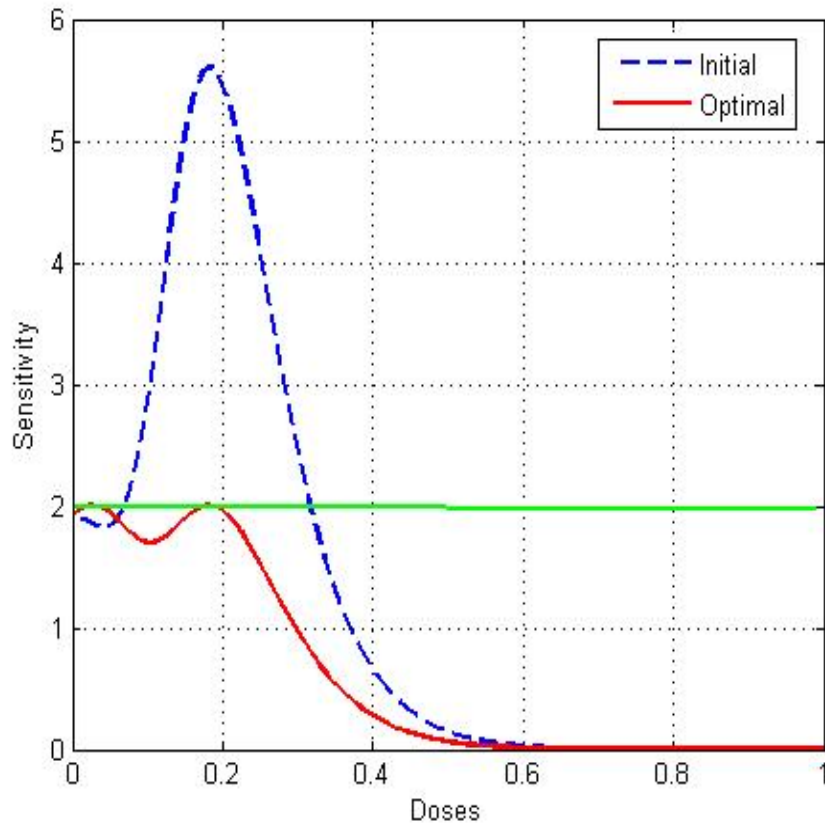
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More References

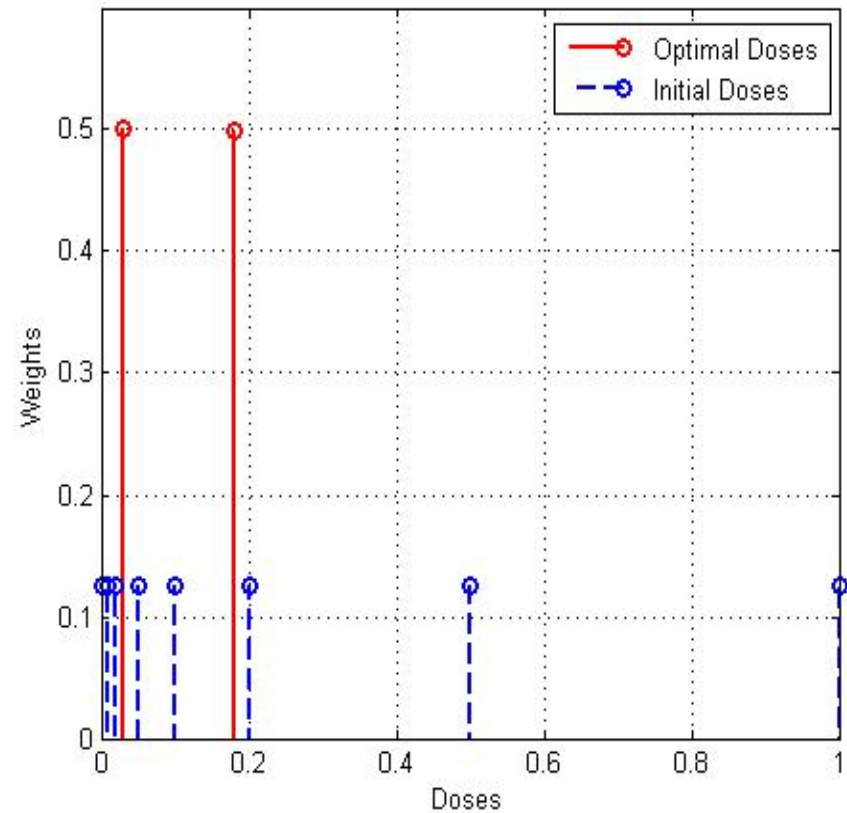
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Back Up Slides: Case Study 3

Sensitivity Function



Initial and Optimal Design



Back Up Slides: Case Study 3

